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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,202	12/04/2001	Keith D. Allen	R-902	6809

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,202	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1,2,13 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-12 and 14-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *06-03-02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Specification

New Fig. 3 and the amendment to the description of Fig. 3 have been entered.

The applications cited in the specification on pg 10, line 19, and pg 11, line 1, will need updated as necessary.

Election/Restrictions

Applicant's election without traverse of Group II, claims 3-12 and 14-25 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Claim 1, 2 and 26-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 3-12 and 14-25 are under consideration in the instant office action.

Claim Objections

Claim 9 is objected to because it is dependent upon claim 1 which is not under consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 3-12 and 14-25 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Claims 6, 7 and 14-24 are directed toward a transgenic animal having a disruption of a Kir5.1 gene, an inwardly rectifying potassium channel. Claims 10 and 25 are directed toward methods of using the mice to identify compounds. The art at the time of filing did not teach mice with a disruption in the Kir5.1 gene. However, the art at the time of filing taught mice with a disruption in GIRK2 (Kir3.2) are indistinguishable from wild-type mice, while *wv/wv* mice, having a single point mutation in the Kir3.2 gene, had extensive cerebellar granule cell death, dopaminergic neuronal loss in the substantia nigra, male infertility, and spontaneous seizures (Signorini, 1997, PNAS, Vol. 94, pg 923-927). Thus, different mutations in inwardly rectifying potassium channels caused different phenotypes. The specification teaches making Kir5.1 -/- mice having dwarfed body shape (pg 53, lines 21-22), decreased body weight, spleen weight and spleen:body weight ratio (pg 54, lines 54), and increased startle response (pg 55, lines 8-11).

The mouse claimed does not have a specific utility. The specification suggests using the mice as a model of disease but does not disclose a specific disease in humans linked to a disruption in Kir5.1 (pg 18, lines 8-9; pg 19, lines 21-23). The specification suggests using the mice to compounds that alter a physiological response in the mice (pg 19, lines 5-20). The specification does not teach a disruption in Kir5.1 correlates to any specific disease or physiological response in humans, specifically

dwarfism, decreased spleen weight, or anxiety as claimed. Using the mice claimed to identify compounds is not specific to the mouse claimed because wild-type mice may be used to identify such compounds. In fact, any mouse can be used to find compounds that increase body weight, increase spleen weight or decrease the startle response. The specification teaches the "open field test" is generic to the hearing processing, sensory and motor processing, global sensory processing and motor abnormalities (pg 54, lines 20-25) as well as sensorimotor processing, attention, anxiety and thought disturbance (pg 54, lines 26-30); therefore, the "open field test" is not specific to any disease. Thus, using the mouse claimed to identify compounds is not specific to that mouse, and the mouse claimed does not have a use that is specific to any disease in humans.

The mouse claimed does not have a substantial utility. Claims 10-11, step c) require administering compounds to the mice and determining whether Kir5.1 gene expression is modulated. Compounds that modulate Kir5.1 expression cannot be found using the mice disclosed because Kir5.1 is not expressed in the mice. Claim 24 requires using identifying an agent that ameliorates a phenotype associated with Kir5.1 by administering compounds to the mice and determining whether a phenotype is ameliorated; however, the specification does not identify any compounds that alter physiological responses using the mice. Therefore, using the mouse to identify compounds is not substantial.

Claim 9 is included because it is directed toward making the mouse, which lacks utility for reasons above. Claims 3-5, 8 and 15, directed toward cells having a disrupted

Kir5.1 gene, and claims 11-12, directed toward using the cells to test compounds, are included because the cells lack a specific and substantial utility for the reasons above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-12 and 14-25 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, the specification does not reasonably provide enablement for any animal, Kir5.1 gene, phenotype, cell, disruption, method of making a transgenic or method of using a transgenic as broadly claimed.

Claims 6, 7 and 14-24 are directed toward a transgenic animal having a disruption of a Kir5.1 gene. Claims 10 and 25 are directed toward methods of using the mice to identify compounds. The art at the time of filing did not teach mice with a disruption in the Kir5.1 gene. However, the art at the time of filing taught mice with a disruption in GIRK2 (Kir3.2) are indistinguishable from wild-type mice while *wv/wv* mice, having a single point mutation in the Kir3.2 gene, had extensive cerebellar granule cell death, dopaminergic neuronal loss in the substantia nigra, male infertility, and

spontaneous seizures (Signorini, 1997, PNAS, Vol. 94, pg 923-927). Thus, different mutations in inwardly rectifying potassium channels caused different results. The specification teaches making Kir5.1 -/- mice having dwarfed body shape (pg 53, lines 21-22), decreased body weight, spleen weight and spleen:body weight ratio (pg 54, lines 54), and increased startle response (pg 55, lines 8-11).

The specification does not enable making or using a transgenic with a wild-type phenotype as encompassed by the claims. The transgenics throughout many of the claims do not recite any phenotype and may, therefore, have any phenotype including wild-type phenotype. The specification does not provide any use for a transgenic having a disruption in Kir5.1 that has a wild-type phenotype.

The specification does not teach how to make any cell having a disruption in a Kir5.1 (claims 3-5). Specifically, claims 4-5 encompass mice and rat cells. "Murine" encompasses mice and rats (http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=murine). The only means of making a cell with a disruption in Kir5.1 taught in the specification is by using mouse embryonic stem cell technology. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught germline transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996, Theriogenology, Vol. 45, pg 57-68) taught transgene expression and the physiological result of such expression in livestock was

not always accurately predicted in transgenic mice (page 62, line 7). The specification fails to provide sufficient guidance to make transgenics other than mice by teaching obtaining ES cells in species other than mice. The specification does not teach the nucleic acid sequence of the Kir5.1 gene in non-mice, non-human species or correlate the Kir5.1 gene in mice to the Kir5.1 gene in other species. The specification does not teach how to make knockout animals other than mice or correlate making knockout mice to other species. Therefore, the specification does not provide adequate guidance for one of skill in the art to make cells having a disruption in Kir5.1 in any species other than mice.

Claim 9 is directed toward a method of making a transgenic mouse having a disruption in Kir5.1 using a cell having a construct with two sequences of Kir5.1, introducing the cell into a blastocyst, implanting the blastocyst into a pseudopregnant mouse which gives birth to chimeric mice, and breeding the chimeric mouse to produce the transgenic mouse. The claim does not require using mouse cells or an embryonic stem cell, which is considered essential to the invention. A mouse ES cell is the only type of cell taught in the specification that can be introduced into a blastocyst and result in a chimeric mouse as claimed. The claim does not require the mouse have a non-wild type phenotype, which is required for reasons cited above. Given the unpredictability in the art taken with the guidance provided in the specification, the cell in a) should be a mouse ES cell, the blastocyst in b) should be a mouse blastocyst, and the transgenic mouse produced should have a genome comprising a homozygous disruption in Kir5.1, wherein said mouse lacks functional Kir5.1.

Claims 10-12 are directed toward methods of screening compounds using a cell or mouse having a disruption in a Kir5.1 gene. Step (c) requires determining whether the expression or function of Kir5.1 is modulated but the mice and cells do not express Kir5.1. The specification does not teach how to determine Kir5.1 expression in mice having a disruption in Kir5.1. While the specification teaches transgenics expressing LacZ, the specification does not teach how to use such mice in an assay to determine whether a compound modulates Kir5.1. Without such a disclosure, the specification does not provide adequate guidance for one of skill to use the mouse disclosed to determine compounds that modulate Kir5.1 expression or function.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-12, 14, 15, 17, 18, 21, 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-11 are indefinite because the mice do not express Kir5.1; therefore, Kir5.1 expression cannot be tested as claimed.

Claim 14 is indefinite because the metes and bounds of what applicants consider "significant" expression cannot be determined.

Claims 17 and 18 are indefinite because "increased anxiety" and "stimulus processing disorder" do not further limit "increased acoustic startle response" in parent claim 16. If claims 17 and 18 do further limit the acoustic startle response or the function of the mouse, it cannot be determined how. The startle test is generic

numerous nervous, muscle and cognitive functions (pg 54, lines 20-30). The limitations do not further limit a characteristic of the mouse because all mice having increased acoustic startle response are considered to have increased anxiety or stimulus processing disorder as claimed.

Claim 21 does not further limit claim 20 because all mice having dwarfism have decreased body weight.

Claim 25 is indefinite because phenotypes "associated" with a disruption in Kir5.1 cannot be determined. While the mice having a disruption in Kir5.1 have dwarfism and increased response to the startle test, it cannot be determined if those phenotypes are "associated" with Kir5.1 in humans. It is unclear if mice having a disruption in a gene mapped to the distal region of mouse chromosome 11 (see Mouri pg 182, Fig. 1, and col. 2, "additional comments") are "associated" with a disruption in Kir5.1.

Claim 25 is indefinite because it does not recite how to determine whether an agent ameliorates a phenotype and neither does the specification. It is unclear what controls are required and how such a determination is made. It is also unclear why a mouse having a disruption in Kir5.1 is required because any mouse can be used to determine whether a compound increases body size, body weight, spleen weight or spleen weight:body weight ratio.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-9 and 14 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Signorini (1997, PNAS, Vol. 94, pg 923-927) in view of Mouri (Genomics, 1998, Vol. 54, pg 181-182).

Signorini taught making a transgenic mouse having a disruption in an inward rectifier protein (GIRK2/Kir3.2) (pg 924, col. 2, 2nd ¶). Signorini did not teach disrupting the Kir5.1 gene in the mice.

However, Mouri taught the nucleic acid sequence of the mouse Kir5.1 gene (GenBank Accession No: AB016197).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having a disruption in an inward rectifier protein as taught by Signorini wherein the inward rectifier protein was Kir5.1 as taught by Mouri. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the Kir5.1 gene instead of the Kir3.2 gene to determine the function of Kir5.1 in the brain *in vivo*.

Thus, Applicants' claimed invention, as a whole is prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER